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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,485	06/29/2004	Martin Bolli	Acteli 18A/E11	4483

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EXAMINER

RAO, DEEPAK R

ART UNIT PAPER NUMBER

1624

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/500,485

Applicant(s)

BOLLI ET AL.

Examiner

Deepak Rao

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 18-32 ☒ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 18-32 ☒ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-9 and 18-32 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypertension, does not reasonably provide enablement for a method of treating all disorders encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims 18-23 recite compositions useful in the treatment of various disorders; claim 24 recites a process to manufacture a composition for the treatment of disorders associated

Art Unit: 1624

with a role of endothelin; claims 25-32 recite methods of treating various disorders. The specification fails to enable one skilled in the art for the recited use in the instant claims.

Note: When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The use disclosed in the specification is as therapeutic agents for the treatment of diseases listed in the claims, which include various diseases including hypertension, coronary diseases, inflammatory disorders, circulatory disorders, cancer, etc. First, the claims cover 'disorders' that are known to exist and those that are yet to be discovered and therefore, the use of the term is extremely broad. Further, there is no description regarding how to identify the subject 'in need of such treatment' in the disclosure. Test procedures for measuring the endothelial inhibitory activity of the compounds is provided on pages 3-9 and results were provided for some of the tested compounds in Table 1. There is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims. The data provided is insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure

Art Unit: 1624

for a Markush group.

Further, there is no disclosure regarding how the patient in need of the treatment is identified and further, how types of inflammatory disorders, cancer, etc. are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art reference on Endothelins (Rubanyi et al.) states that “Despite these speculations, however, the physiological and pathophysiological significance of ETs remains to be established. Several key questions need to be analyzed and answered.” This establishes the unpredictability of the art regarding the pharmacological activity of the endothelin receptors and the disclosure does not direct the skilled artisan to any art that provides treatment of all diseases associated with the role of endothelins.

A ‘cancer’ (or tumor or proliferative disease) is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “silver bullet” is

Art Unit: 1624

contrary to our present understanding of oncology. Cecil Textbook of Medicine states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Enablement for the scope of "treatment of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It

Art Unit: 1624

may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as

Art Unit: 1624

the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims recite '**prevention** of restenosis after balloon or stent angioplasty' (see for example, claim 29) and therefore, the instant claims include “**prevention**” of the diseases which is not remotely enabled. Based on the ET_A and ET_B inhibition data provided for some of the compounds of the examples, the instant compounds are disclosed to be useful in the “prevention” of cancer, atherosclerosis, etc. for which applicants provide no competent evidence. “To prevent” actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the “prevention” effect. It is inconceivable from this *in vitro* data, as to how the claimed compounds can not only treat but also “prevent” a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as “showing” such utility, and not “warranting further study”). Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

Art Unit: 1624

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 18-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims recite “Compounds” or “The compounds” through out the claims. The plural recitation “compounds” is not proper Markush language in a claim. As the claims are drawn specifically to: ' A compound of formula I ', it should be recited as such. Replacing the recitation “Compounds” (in claim 1) with -- A compound -- and amending the dependent claims appropriately is suggested.

Allowable Subject Matter

Claims 1-9 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action. The closest reference of record, WO 98/57938 teaches N-pyrimidinylalkanesulfonamide compounds useful as endothelin antagonists, however, the reference compounds contain a terminal cyclic group A which is not present in the instantly claimed compounds. The reference does not teach or fairly suggest the instantly claimed compounds.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

Art Unit: 1624

system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

December 6, 2006